Internal Dosimetry assessment for monoclonal antibodies and antibody fragments labeled by Lutetium-177

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Abstract: In this research, the behaviour of monoclonal antibodies (MAbs) and their fragments labeled by ^{177}Lu after injecting into the body is simulated for diagnostic and therapy. The absorbed doses in organs and tissues with maximum radiation exposure are presented. On the base of reference data in the literature, a biokinetic model is built-in for MAb and their fragments. The cumulative activity of ^{177}Lu in organs and tissues per Bq of administered activity is calculated. Spleen, liver, and red bone marrow have the highest doses when ^{177}Lu associated with intact monoclonal antibodies is injected into human body. The estimated doses on these organs are 1.95, 1.17 and 0.54 mGy/MBq, respectively. For the fragments of monoclonal antibodies is considered with ^{177}Lu, the most exposed organs are the kidneys with the doses of 0.78 mGy/MBq for F(ab')) and 1.27 mGy/MBq for $F(ab')_2$.

1. Introduction

One of the most promising drugs in the therapy of oncological diseases are considered to be short-lived β-emitting radionuclides. Such nuclides apply ^{177}Lu. ^{177}Lu is a beta radiating nuclide with the energy of 0.49 MeV and a half-life of 6.7 days (161 h). The mileage of the particles in tissue does not exceed 2.5 mm. ^{177}Lu also emits low-energy γ-rays 384 and 176 Kev with an intensity of 9.1% and 12.3%, respectively. This allows scintigraphy in the process of therapy.

During recent years, a new generation of more realistic internal dosimetry models, including the Human Respiratory Tract Model [1] and recycling systemic models for actinides [2,3] had developed by ICRP. The 3rd European Intercomparison Exercise on Internal Dose Assessment carried out in the framework of EULEP/EURADOS/UIR concerted action "Environmental and occupational dosimetry: an integrated approach to radiation protection covering radioecology, dosimetry, and biological effects" provided special insight into the effects of the new models and the choice of input parameters on the assessment of internal doses from monitoring results [4].

It also took into account some aspects which were not considered in previous exercises, such as air monitoring, natural radionuclides, exposure of the public, artificially created cases and artificially reduced information. Seven case scenarios were distributed, dealing with ^{3}H, ^{90}Sr, ^{125}I, ^{137}Cs, ^{210}Po, ^{238}U and ^{239}Pu, and covering different intake scenarios and all monitoring techniques.

The results were received from 50 participants, 43 representing 18 European countries and 7 from countries outside Europe. Thus it was by far the largest exercise of this type carried out to date. Most participants attempted more than half of the cases. Thus, on average there were 35 responses per case with a total of about 240 answers, giving a good overview of the state of the art of internal dosimetry. The results in terms of intake and committed effective dose appeared to be close to lognormally distributed with geometric standard deviation ranging from 1.15 for the cases dealing with 3H and ^{137}Cs, up to 2.4 for the cases dealing with ^{239}Pu. These figures reflect large differences in the individual results which varied in the worst cases within a range of five orders of magnitude.

A key feature of the exercise was a workshop, involving most of the participants, at which each case and the various approaches were discussed. Several reasons for the differences in the results were identified, including different assumptions about the pattern of intake, and the choice of model. The most important conclusion of the exercise was the need to develop agreed guidelines for internal dose evaluation procedures in order to promote the harmonization of assessments between organizations and countries, which has basic importance in EU countries. This was the reason to launch the IDEAS project in the 5th EU Framework Programme (EU Contract No. FIKR-CT2001-00160).

The dosimetry for ^{177}Lu -labeled monoclonal antibodies and fragments has been studied insufficiently. The purpose of this work is the assessment of radiation exposure of patients after the injection of ^{177}Lu -labeled monoclonal antibodies and fragments for PET visualization.

2. Methods

In the practice of using radiopharmaceuticals, both intact monoclonal antibodies and their fragments are used. In the ICRP Publication 128 [5], the data on the dynamic behavior of the antibodies and fragments labeled with the radionuclides ^{99m}Tc, ^{131}I, ^{111}In, ^{123}I are presented, but the data for ^{89}Zr or ^{177}Lu is absent. It is necessary to note that all the coefficients, which are given in Reference [5], for ^{99m}Tc, are the same for all listed radionuclides. This is due to the fact that the biological rates of radionuclide removal from an organ are determined not by the nuclide properties, but by the properties of the carrier (MAb) to which they are attached [6, 7].

The purpose of this study is a general assessment of radiation exposure of tissues and organs, without connection to specific monoclonal antibodies or their fragments. Therefore, according to the averaged data for calculations, the following are the values of the half-life times of the radiotracer transfer from the bloodstream to organs and tissues 50 h for intact MAb, 12h for fragments of MAb $(ab)'_2$ and 6 h for fragments of MAb $(ab)'$.

There are some common features in the behavior of antibodies. After intravenous injection, the highest activity is observed in organs with high vascular perfusion, that is, in the liver, spleen, bone marrow and kidneys [5].

In order to calculate the absorbed dose for organs and tissues, it is possible to use two approaches. In the first one, based on the transfer activity fraction from blood to organs and removal activity rate from organs and the excretion rate, the WinAct program (https://www.ornl.gov/crpk/software) is used to calculate the cumulated activity in organs and tissues [8].

The output results from the WinAct program are used as input data to IDAC 2.1 software, an internal dosimetry program for nuclear medicine based on the ICRP adult reference voxel phantoms [9, 10]. As a result, the absorbed doses to organs and tissues are estimated.

3. Results

Figures 1-2 show the dependence of the activity of radiopharmaceutical in various organs after intravenous injection. The figures show that the intact MAb labeled with ^{177}Lu is accumulated in the organs relative to excretion of the radionuclide from the same organs. In addition, the figures show that the fragments of MAb labeled with ^{177}Lu are characterized by both faster accumulations in the organs and a faster excretion of the radionuclide in comparison to intact MAb. In order to assess the potential threat to the patient from exposure to radiopharmaceuticals use, the absorbed doses were calculated for the organs with the maximal accumulation of the labeled complex: the kidneys, red bone marrow, spleen, and liver. Since the ^{177}Lu emits its own gamma rays and gamma rays as a result of positron annihilation, it was also necessary to calculate the absorbed doses for the adjacent organs (the targeted organs), which are exposed by the source organ. The injection is administered directly into the blood that circulates throughout the body, and, largely, in the lungs, so the assessment of the absorbed dose from this source is required.

The calculations were made for three types of injections: intact antibody, as well as the fragments of antibodies F (ab)'2 and F (ab)', labeled ^{177}Lu. All calculations were made of the absorbed doses administered for injection 1 activity in Bq. The data on the residence time of radionuclide in organs and tissues were used as the input data to the internal dosimetry program IDAC 2.1 [11] for diagnostic nuclear medicine based on the ICRP adult reference voxel phantoms [10].

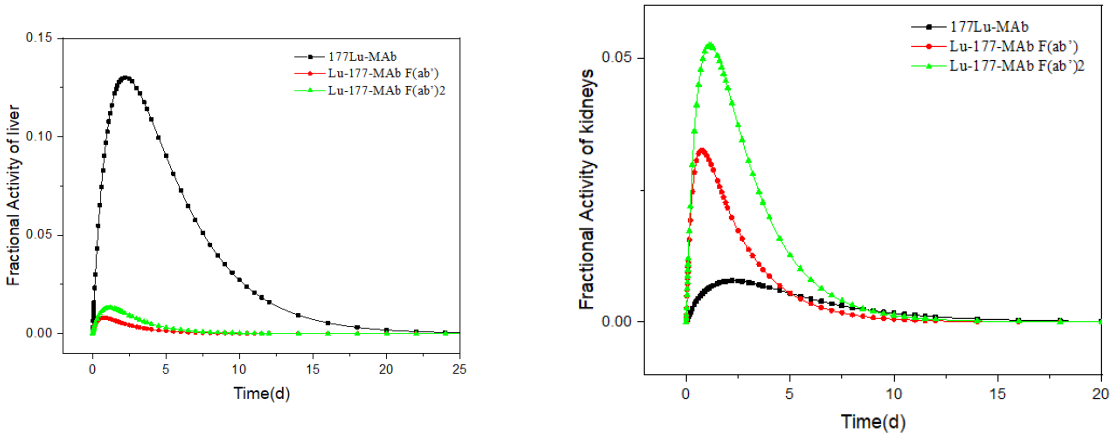

Figure 1. Dependence of the activity of radiopharmaceutical in the liver and kidneys after intravenous injection.

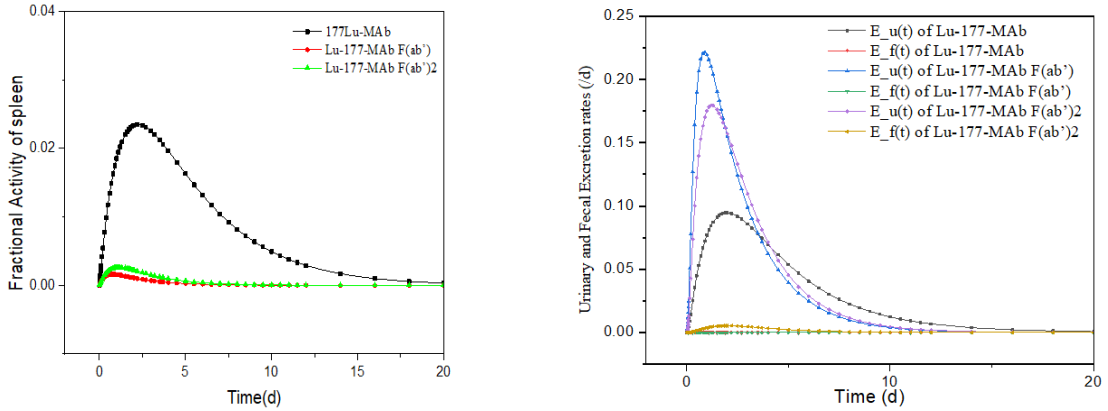

Figure 2. Fractional activity as a function of time (h) for Spleen and Excreting from WinAct.

As a result, the absorbed doses to organs and tissue are estimated. The data on dose coefficients for organs and tissues are presented in figure 3.

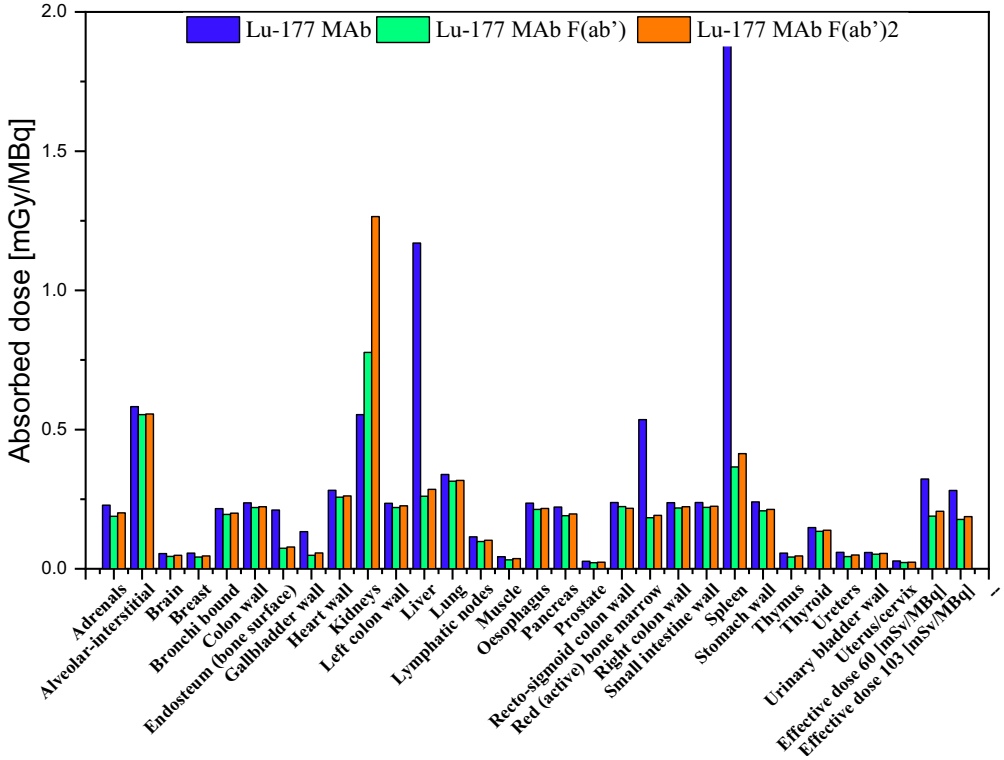

Figure 3. Bar chart plots of the estimated absorbed dose in mGy/MBq of Lu-177 MAb and its fragments to the mean organs for Adulate human, calculated by WinAct program and IDAC 2.1.

4. Conclusion

- The biokinetic model is constructed for the dynamics of a radiopharmaceutical based on ^{177}Lu, labeled with antibodies behavior in the body.
- The dependences of the distributed activity in organs and tissues in time of its presence are presented, and the most irradiated organs are revealed.
- For the most exposed organs, the dose coefficients on the unit of the injected activity were calculated.
- It is shown that for the intact MAb administrated ^{177}Lu in the body the most exposed organs are the spleen, liver, kidneys and red marrow when administered ^{177}Lu bound to fragments of MAb F(ab)′2 – the kidneys, spleen, liver and red marrow. With the injection of ^{177}Lu bound to fragments of MAb F (ab)′ the kidneys get the highest doses.
- When using radiopharmaceuticals in the form of the intact antibodies with the activity of 75 MBq, the absorbed dose in the spleen will be 146.3 mGy, and in the liver 87.75 mGy. The maximum dose to the kidneys at the same injected activity, using the fragments F(ab)′$_2$, will be 95.3 mGy.
- Although ^{177}Lu, labeled with intact antibodies can use for spleen therapy liver gets a relatively high dose, it should be taken care of when used.

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